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Hereditary Multiple Exostoses: Confirmation of Linkage to Chromosomes 8 and 11

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Hereditary multiple exostoses (EXT) is an autosomal dominant disorder characterized by the formation of cartilage capped prominences that develop from the epiphyses of the long bones. EXT is heterogeneous with three different locations currently identified on chromosomes 8, 11, and 19. Recently, we identified and studied 12 large multigenerational EXT families. Linkage analyses demonstrates that 6 of these families map to 8q24 and 6 to 11p. None of the families map to the chromosome 19 locus. The results suggest that there are two major loci, on chromosomes 8 and 11, involved in the cause of EXT. The locus on chromosome 19 remains to be confirmed. © 1996 Wiley-Liss, Inc.

KEY WORDS: hereditary multiple exostoses, linkage study, genetic study, chromosome 8, chromosome 11, chromosome 19, haplotype, Lager Giedion syndrome, EXT

INTRODUCTION

Hereditary multiple exostoses (EXT) (MIM 133700) is a condition characterized by bony overgrowth at the ends of the long bones which results in bony protuberances [Solomon, 1963]. Orthopedic complications, such as limb length inequalities, bowing, bony synostosis, impaired articular function and short stature, are common associated problems [Schmale et al., 1994; Luckert-Wicklund et al., 1995]. The most serious complication is malignancy which occurs in less than 5% of EXT individuals. It has been suspected that EXT would map to the Langer-Giedion region (8q24.11–24.13), as the exostoses in Langer-Giedion syndrome (LGS) are indistinguishable from those seen in hereditary multiple exostoses. Figure 1a,b are radiographs from individuals with EXT and LGS, respectively. As can be seen, the two radiographs are very similar. A study by Le Merrer et al. [1992] was unable to detect linkage to RFLP markers near the LGS region. Subsequently, Cook et al. [1993] demonstrated not only that there was strong evidence for linkage of EXT to chromosome 8q24.11–24.13 region, but that there were clearly families (30%) which did not map to this region. In that study, we were able to narrow the region on 8q to an approximate 7 cM region between D8S85 and D8S199. Subsequently, two additional EXT loci were reported: a locus mapping to the pericentromeric region of chromosome 11 was reported by Wu et al. [1994] (EXT2) and a locus on 19p was reported by Le Merrer et al. [1994] (EXT3).

The distribution of the three types of EXT is currently unknown. We undertook this linkage study to assess whether genes on chromosome 11 or chromosome 19 were responsible for EXT in families which did not map to chromosome 8.

METHODS

Twelve multigenerational families with EXT were ascertained from the Medical Genetics Clinic of the University of Texas Medical School and Shriners Hospital—Houston unit and City Hospital, Nottingham, England. Pedigrees of these families are presented in Figure 2. Relatives were evaluated by clinical and radiographic examinations to document the presence or absence of exostoses. Family 9 has an affected person who has developed a pelvic chondrosarcoma. The description and molecular studies in this family are the subject of a separate report [Hecht et al., 1995]. Only one family (12) was available from our previous study. DNA samples were prepared by standard methods [Sambrook et al., 1989].

The 14 STR PCR markers from chromosomes 8, 11, and 19 used in the analysis are listed in Table I. All families were typed for a subset of 11 markers

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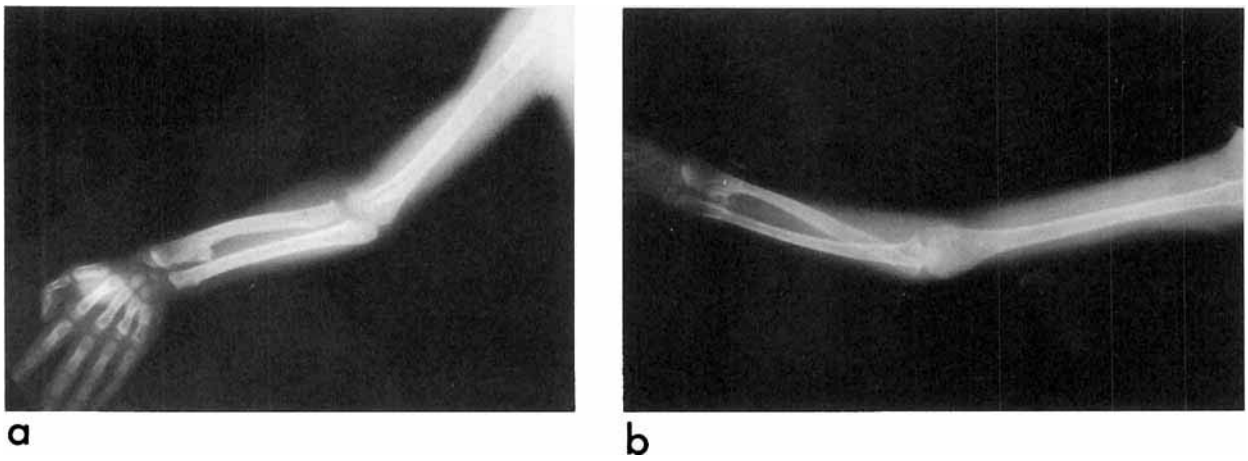


Fig. 1. **a:** Upper limb from EXT patient demonstrating multiple exostoses. **b:** Upper limb from LGS patient with multiple exostoses.

(D8S200, D8S85, D8S199, D8S198, D11S935, D11S905, D11S1313, D11S554, D19S216, D19S413, and D19S221). Typing of additional markers, D8S592 and D8S527, in family 8 and, D11S1355 and D11S916, in family 9 was done in order to localize the recombinations. PCR was performed using standard techniques [Sambrook et al., 1989]. The gels were silver stained using the Gelcode system (Pierce) [Hecht et al., 1993].

Two point LOD scores between EXT and the tested markers were generated using the MLINK program of the LINKAGE package (version 5.03) [Lathrop et al., 1984]. Multipoint analyses were conducted using a modified version of LINKMAP from the LINKAGE program [Cottingham et al., 1994]. An autosomal dominant mode of inheritance was assumed for EXT with 95% penetrance [Cook et al.,1993]. Individuals marrying into the family were considered to be homozygous normal. Distances for multipoint analyses were sex-averaged estimates based on the CEPH reference pedigrees [Tomfohrde et al., 1992; Gyapay et al., 1994]. Two point homogeneity tests were conducted using HOMOG [Ott, 1991]. Results from the multipoint analysis on chromosomes 8 and 11 were evaluated for homogeneity using HOMOG3R [Ott, 1991]. All two point analyses and homogeneity tests were done on a Pentium based personal computer. The multipoint analyses were run on a Sun/SPARC workstation.

The use of STRs with their high heterozygosities increases the probability that an individual family will be informative. However, multipoint analysis of these markers can be computationally difficult. For this reason, the alleles were downcoded on a family-by-family basis. Comparison of the results from the two-point analyses of the down-coded data to the original data did not detect any loss of information.

RESULTS

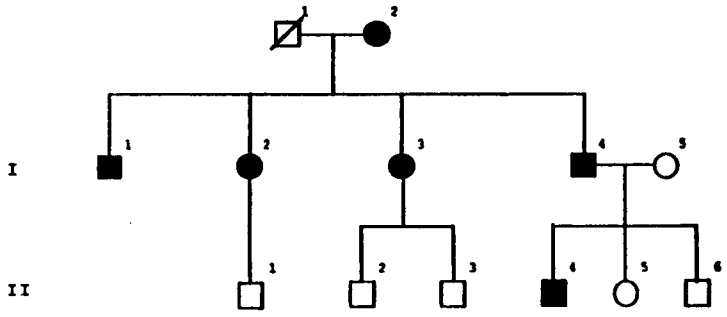
Results of the two point linkage analysis between EXT and markers on chromosomes 8, 11, and 19 are presented in Tables II, III, and IV, respectively. Significant LOD scores were obtained between EXT and D8S85, D8S199, D8S198, D11S905, and D11S554. None of the markers on chromosome 19 demonstrated significant linkage to EXT. Homogeneity was rejected for D8S198 ($\chi^2 = 5.28, P < 0.025$), D11S905 ($\chi^2 = 17.47, P < 0.001$), and D11S554 ($\chi^2 = 19.42, P < 0.001$).

Multipoint analysis was run for markers on chromosomes 8 and 11 (Figs. 3, 4). When all families were included in the analyses, linkage to the regions between both sets of reported flanking markers was excluded. The resulting data were evaluated using HOMOG3R [Ott, 1991]. This examines the data under the hypothesis that there are at least two family types, each type mapping to a locus on a different chromosome. It also allows for a third type which maps to an as yet unknown locus. The results are summarized in Table V. Homogeneity was clearly rejected, with the model allowing for heterogeneity being 9.1×10^{19} times more likely than the model with homogeneity. The most likely model of 50% of the families mapping to chromosome 8 and 50% of the families mapping to chromosome 11 was 5.4×10^{8} times more likely than the next most likely model of 60% of the families mapping to chromosome 11 and the remaining 40% mapping to an unknown locus. The conditional probabilities of linkage for each family are presented in Table VI. Notably, the lowest probability of a family mapping to its most likely chromosome is over 90%. When only those families with a low probability of mapping to the other chromosome, based on HOMOG3R results, were included in the multipoint analysis, linkage to the regions is clearly supported (Figs. 3, 4).

DISCUSSION

The multiple exostoses seen in EXT are indistinguishable from those seen in the LGS. Most cases of LGS result from a deletion which includes 8q24.11–q24.13 [Buhler et al., 1984]. Additionally, a patient with multi-

Family 2



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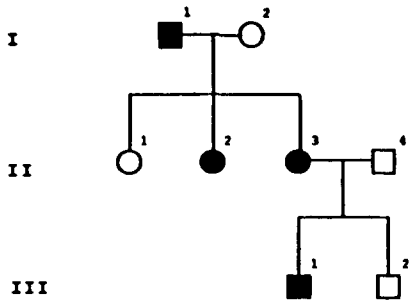
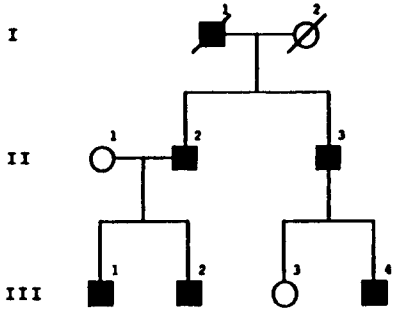
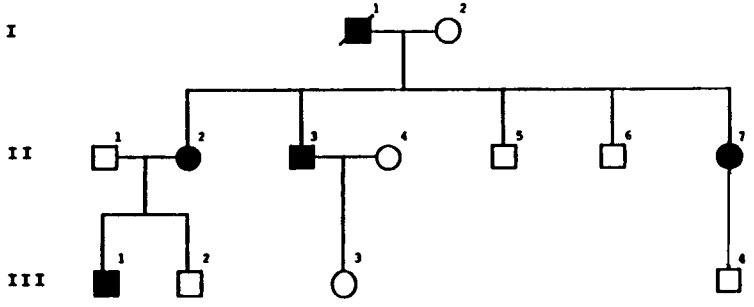


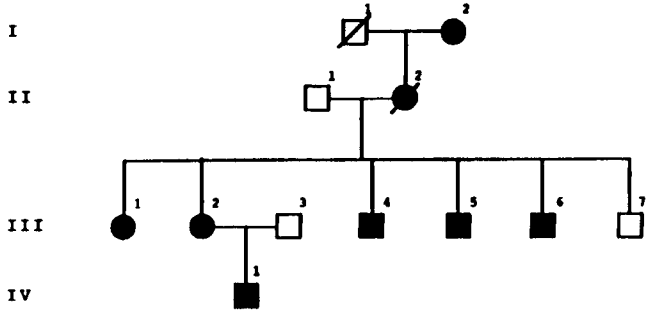
Family 4



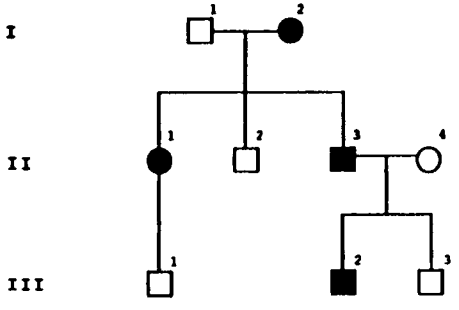
Family 5



Family 6



Family 7



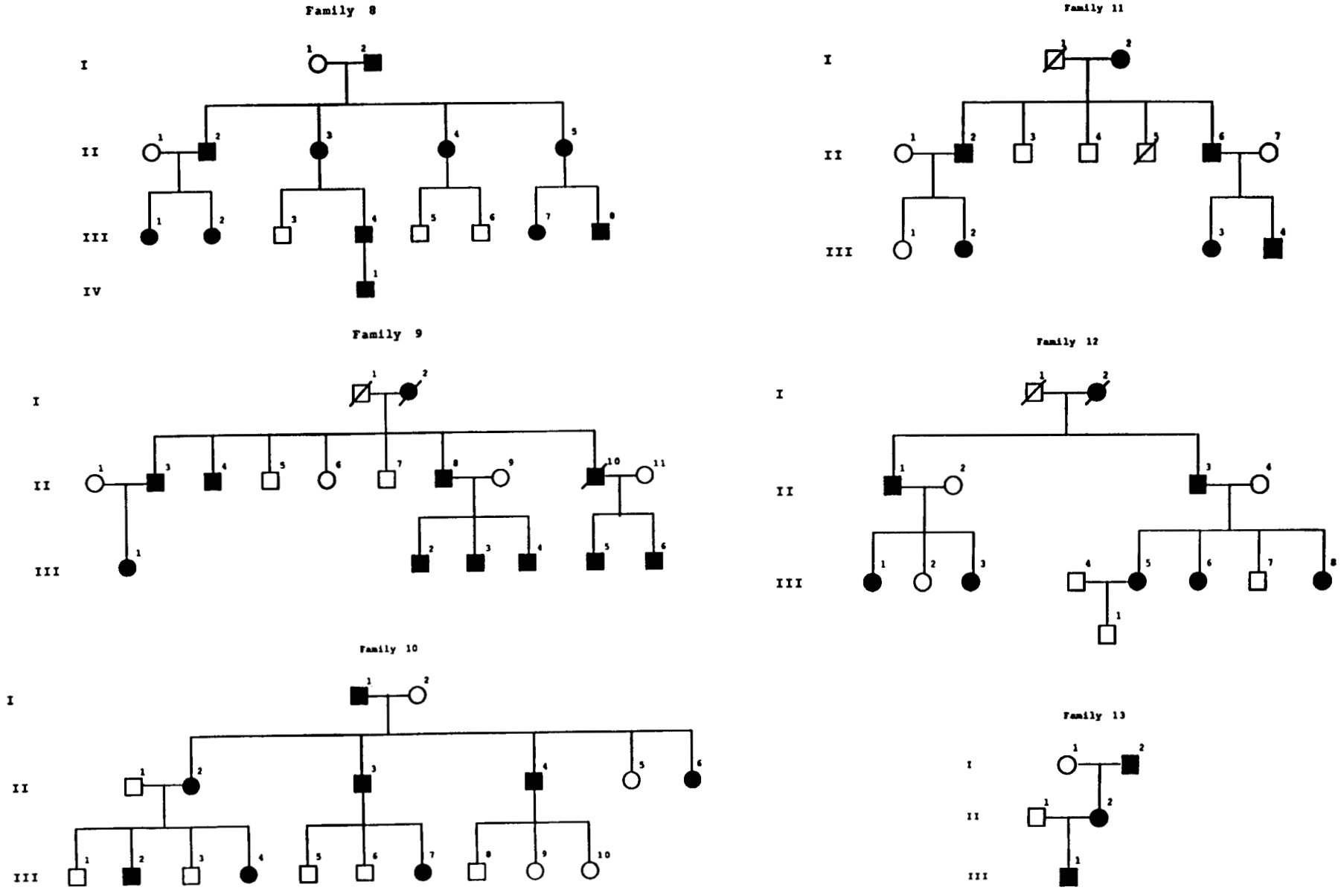


Fig. 2. Pedigrees of the 12 EXT families included in this study. Individuals with EXT are indicated by a darkened symbol. Individuals with a slash (/) are deceased and DNA was not available. Unrelated spouses who were not available have been removed from the pedigrees.

TABLE I. STR PCR Markers and Allele Sizes

Marker	Allele size
Chromosome 8[a]	
D8S200	182–196
D8S85	72–80
D8S592	148–156
D8S527	272–282
D8S199	208–230
D8S198	155–167
Chromosome 11[b]	
D11S935	196–208
D11S905	208–228
D11S1355[c]	141–147
D11S554	174–254
D11S1313	184–204
D11S916[c]	135–150
Chromosome 19[b]	
D19S216	179–191
D19S413	69–91
D19S221	191–211

[a] Markers in order 8 cent-8qter as per M. Wagner, 1995, unpublished data.
[b] Order of markers as published in reference 21.
[c] Used to establish recombination.

ple exostoses has been described with a balanced translocation t(8:11)(q24.11;p15.5) [Ogle et al., 1991]. It was hypothesized that LGS is a contiguous gene syndrome and EXT would map to the same region. Although the initial report by Le Merrer et al. [1992] suggested that EXT did not map to this region, we were able to demonstrate that some, but not all, EXT families clearly map to the LGS region [Cook et al., 1993]. Additional patients with non-familial EXT and chromosome rearrangements and deletions in this region subsequently were reported [Mertens et al., 1994; Yoshiura et al., 1994]. Le Merrer et al. [1994] and Wu et al. [1994] then demonstrated linkage to chromosomes 19 and 11, respectively. As all of their families were European, it was not clear what percentage of United States families would map to these chromosomes.

We have confirmed the mapping of EXT to chromosomes 8q and 11p, but have been unable to confirm mapping of EXT3 to 19p. Based on both the two-point and multipoint data, families 2, 3, 5, 8, and 12 have high probabilities of mapping to chromosome 8, while families 4, 7, 9, 10, 11, and 12 demonstrate evidence for linkage to chromosome 11. The two-point analyses of family 6 yields results which are compatible with linkage to either 8 or 11, although higher LOD scores are generated for markers on chromosome 8 than those on chromosome 11. HOMOG3R predicts that this family is linked to chromosome 8.

We had previously localized EXT1 to the 6.6 cM region flanked by D8S85 and D8S198 [Cook et al., 1993]. We were able to refine this position by the identification of a recombination in family 8. Family 8 had a recombination in the region flanked by D8S85 and D8S199, which is the region to which we previously mapped the EXT1 locus [Cook et al., 1993]. Part of this family was typed for the two additional markers which map to this region. As can be seen from Figure 5, affected individual IV-1 has inherited alleles from his unaffected paternal grandfather at D8S200, D8S85, and D8S592, while he inherited alleles from his affected paternal grandmother at D8S527, D8S199, and D8S198. In combination with our previous findings, this suggests a placement for EXT1 between D8S592 and D8S199. This is in contrast to the findings of Le Merrer et al. [1994] who placed the locus distal to D8S199. However, their positioning was based on a sample that included several families which could also map to chromosome 19. Localizing the gene for EXT1 using only families with a low probability of mapping to chromosome 19 might place the gene in a position consistent with our findings. Placement of EXT1 centromeric to D8S199 is supported by Ludecke et al. [1995] who studied EXT patients with chromosome abnormalities using YAC contigs. Their data suggest that EXT1 lies 1.5 to 2.0 Mb centromeric to D8S199.

Family 9 had a recombination in the region flanked by D11S905 and D11S554 (Fig. 6). Unaffected individual II-6 shared alleles at D11S935 and D11S905 with his affected sibs, II-2, II-3, and II-7, suggesting a placement of EXT2 distal to D11S905. Further investigation of this family detected a submicroscopic deletion between D11S905 and D11S554, at D11S903, in all affected individuals. Details of this and related studies in this family are presented elsewhere [Hecht et al., 1995].

Le Merrer et al. [1994] estimated that in their study of 21 EXT families, 65% of the families map to 8q and 35% map to 19p. Wu et al. [1994] studied only two families, both of which mapped to chromosome 11. We have been able to confirm the mapping of EXT to chromosome 11; however, none of our families demonstrated linkage to markers on chromosome 19. Family 12 had previously been excluded from chromosome 8. EXT in 11 families was mapped confidently to either chromosome 8 (5) or chromosome 11 (6). One family, family 6, gave results consistent with linkage to either 8 or 11, but an analysis of the multipoint results clearly favored a chromosome 8 placement. Clinically, the two sets of families are indistinguishable. This suggests that approximately 50% of the families in the U.S. with EXT will map to chromosome 8 and approximately 50% map to chromosome 11. This is in agreement with our original study which estimated that approximately 70% (95% C.I. 26–96%) of families map to chromosome 8 [Cook et al., 1993]. While none of our families map to chromosome 19, it is possible that a gene at this location may still account for a small portion of families.

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TABLE II. Two Point LOD Scores for Chromosome 8 Markers and EXT Families

	Recombination fraction (θ)						
Family	0.00	0.001	0.01	0.05	0.10	0.20	0.30
D8S200							
2	−1.74	−1.72	−1.59	−1.18	−0.86	−0.47	−0.24
3	0.58	0.58	0.57	0.53	0.49	0.39	0.28
4	0.17	0.17	0.16	0.14	0.12	0.07	0.03
5	2.30	2.29	2.26	2.10	1.90	1.45	0.96
6	−∞	−0.91	0.06	0.65	0.81	0.81	0.64
7	−1.16	−1.14	−1.02	−0.65	−0.38	−0.09	0.02
8	−∞	0.08	1.04	1.56	1.63	1.41	1.01
9	−∞	−2.71	−1.71	−1.02	−0.72	−0.38	−0.16
10	−∞	−5.51	−3.45	−1.89	−1.19	−0.53	−0.20
11	−1.02	−1.01	−0.94	−0.73	−0.55	−0.34	−0.19
12	−∞	−3.29	−2.18	−1.17	−0.68	−0.26	−0.12
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Totals	−∞	−13.17	−6.80	−1.66	0.55	2.05	2.01
D8S85							
2	1.85	1.85	1.81	1.66	1.46	1.04	0.59
3	1.16	1.16	1.14	1.05	0.93	0.69	0.44
4	0.96	0.95	0.93	0.84	0.73	0.49	0.26
5	1.44	1.43	1.41	1.31	1.17	0.87	0.54
6	−∞	−0.91	0.06	0.65	0.81	0.81	0.64
7	−1.16	−1.14	−1.02	−0.65	−0.38	−0.09	0.02
8	−∞	−0.77	0.19	0.77	0.90	0.83	0.58
9	−∞	−2.45	−1.46	−0.79	−0.51	−0.23	−0.08
10	−∞	−1.59	−0.56	0.18	0.44	0.53	0.41
11	−∞	−2.00	−1.00	−0.31	−0.05	0.11	0.12
12	−∞	−3.82	−2.70	−1.64	−1.09	−0.54	−0.26
13	0.30	0.30	0.29	0.27	0.25	0.20	0.14
Totals	−∞	−7.01	−0.89	3.34	4.68	4.73	3.44
D8S199							
2	1.78	1.77	1.74	1.58	1.38	0.95	0.50
3	1.16	1.16	1.14	1.05	0.93	0.69	0.44
4	0.41	0.41	0.40	0.34	0.27	0.15	0.06
5	1.03	1.03	1.02	0.96	0.88	0.71	0.52
6	2.08	2.08	2.05	1.93	1.76	1.41	1.01
7	−0.72	−0.71	−0.65	−0.46	−0.31	−0.15	−0.06
8	1.68	1.68	1.65	1.54	1.39	1.06	0.70
9	−∞	−2.763	−0.80	0.39	0.74	0.79	0.53
10	−∞	−3.98	−1.95	−0.51	0.05	0.43	0.46
11	−∞	−8.25	−5.19	−2.95	−1.96	−1.01	−0.51
12	−∞	−2.81	−1.66	−0.67	−0.26	0.01	0.06
13	0.30	0.30	0.29	0.27	0.25	0.20	0.14
Totals	−∞	−10.07	−1.95	3.50	5.15	5.28	3.87
D8S198							
2	0.90	0.90	0.88	0.81	0.72	0.51	0.29
3	1.16	1.16	1.14	1.05	0.93	0.69	0.44
4	−0.84	−0.83	−0.77	−0.57	−0.40	−0.20	−0.08
5	2.30	2.29	2.26	2.10	1.90	1.45	0.96
6	0.41	0.41	0.41	0.37	0.33	0.24	0.15
7	−1.16	−1.1460	−1.02	−0.65	−0.38	−0.09	0.02
8	2.94	2.93	2.88	2.67	2.39	1.80	1.19
9	−∞	−3.65	−1.69	−0.43	−0.01	0.20	0.14
10	−∞	−9.65	−6.47	−3.82	−2.51	−1.20	−0.53
11	−∞	−2.53	−1.479	−0.63	−0.25	0.06	0.15
12	−0.47	−0.46	−0.36	−0.06	0.11	0.20	0.13
13	0.30	0.30	0.29	0.27	0.25	0.20	0.14
Totals	−∞	−10.28	−3.91	1.12	3.08	3.89	3.04

TABLE III. Two Point LOD Scores for Chromosome 11 Markers and EXT Families

	Recombination fraction (θ)						
Marker	0.00	0.001	0.01	0.05	0.10	0.20	0.30
D11S935							
2	−∞	−8.75	−5.63	−3.19	−2.05	−0.95	−0.40
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4	0.93	0.93	0.91	0.82	0.70	0.46	0.24
5	−∞	−4.85	−3.66	−2.37	−1.62	−0.82	−0.38
6	0.03	0.03	0.01	−0.07	−0.18	−0.36	−0.39
7	−∞	−2.55	−1.55	−0.85	−0.56	−0.28	−0.13
8	−∞	−3.41	−1.44	−0.18	0.24	0.47	0.42
9	−∞	−1.53	−0.55	0.05	0.24	0.29	0.20
10	0.86	0.85	0.84	0.79	0.72	0.58	0.41
11	−∞	−0.95	0.01	0.59	0.74	0.71	0.55
12	−∞	−2.08	−1.09	−0.42	−0.17	−0.04	0.03
13	−∞	−2.69	−1.69	−1.00	−0.69	−0.39	−0.22
Totals	−∞	−25.02	−13.85	−5.84	−2.64	−0.28	0.33
D11S905							
2	−∞	−8.22	−5.17	−2.91	−1.90	−0.93	−0.43
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4	1.16	1.16	1.14	1.03	0.90	0.62	0.34
5	−∞	−5.87	−4.61	−3.10	−2.18	−1.16	−0.57
6	0.10	0.10	0.12	0.17	0.19	0.17	0.12
7	1.44	1.43	1.41	1.31	1.17	0.88	0.57
8	−∞	−9.83	−5.83	−3.06	−1.91	−0.87	−0.37
9	1.94	1.95	1.97	1.97	1.86	1.47	0.94
10	3.52	3.52	3.47	3.22	2.91	2.23	1.49
11	2.04	2.04	2.00	1.86	1.68	1.28	0.84
12	2.02	2.02	1.98	1.83	1.63	1.20	0.75
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Totals	−∞	−11.68	−3.50	2.33	4.36	4.92	3.69
D11S1313							
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	−∞	−4.56	−2.42	−1.42	−0.74	−0.21	−0.08
4	−0.20	−0.19	−0.13	0.01	0.08	0.10	0.06
5	−∞	4.96	−3.77	−2.47	−1.71	−0.88	−0.42
6	−∞	−4.21	−2.23	−0.90	−0.39	0.01	0.12
7	1.44	1.43	1.41	1.31	1.17	0.88	0.57
8	−∞	−9.93	−5.94	−3.20	−2.06	−1.01	−0.47
9	−∞	0.24	1.19	1.68	1.70	1.40	0.89
10	1.80	1.80	1.78	1.66	1.51	1.19	0.83
11	−∞	−0.95	0.01	0.59	0.74	0.71	0.55
12	0.44	0.44	0.43	0.40	0.35	0.25	0.16
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Totals	−∞	−18.75	−8.66	−1.66	0.93	2.46	2.23
D11S554							
2	−∞	−8.96	−5.84	−3.38	−2.23	−1.08	−0.49
3	−∞	−4.81	−2.82	−1.46	−0.90	−0.40	−0.16
4	1.11	1.11	1.09	0.99	0.86	0.59	0.33
5	−∞	−5.87	−4.61	−3.10	−2.18	−1.16	−0.57
6	−∞	−0.91	0.06	0.65	0.81	0.81	0.64
7	1.44	1.43	1.41	1.31	1.17	0.88	0.57
8	−∞	−15.44	−9.40	−5.09	−3.25	−1.53	−0.67
9	2.96	2.96	2.91	2.70	2.42	1.81	1.13
10	2.74	2.74	2.76	2.73	2.58	2.10	1.47
11	1.56	1.56	1.53	1.39	1.21	0.82	0.45
12	2.28	2.27	2.24	2.07	1.85	1.38	0.88
13	−∞	−2.69	−1.69	−1.00	−0.69	−0.39	−0.22
Totals	−∞	−26.60	−12.36	−2.20	1.63	3.84	3.35

TABLE IV. Two Point LOD Scores for Chromosome 19 Markers and EXT Families

	Recombination fraction (θ)						
Marker	0.00	0.001	0.01	0.05	0.10	0.20	0.30
D19S216	−∞	−27.56	−16.99	−8.40	−4.52	−1.28	−0.17
D19S413	−∞	−47.21	−29.47	−15.49	−9.14	−3.49	−1.17
D19S221	−∞	−58.01	−37.93	−21.66	−13.97	−6.56	−2.93
D19S226	−∞	−56.40	−33.87	−16.99	−9.69	−3.42	−0.97

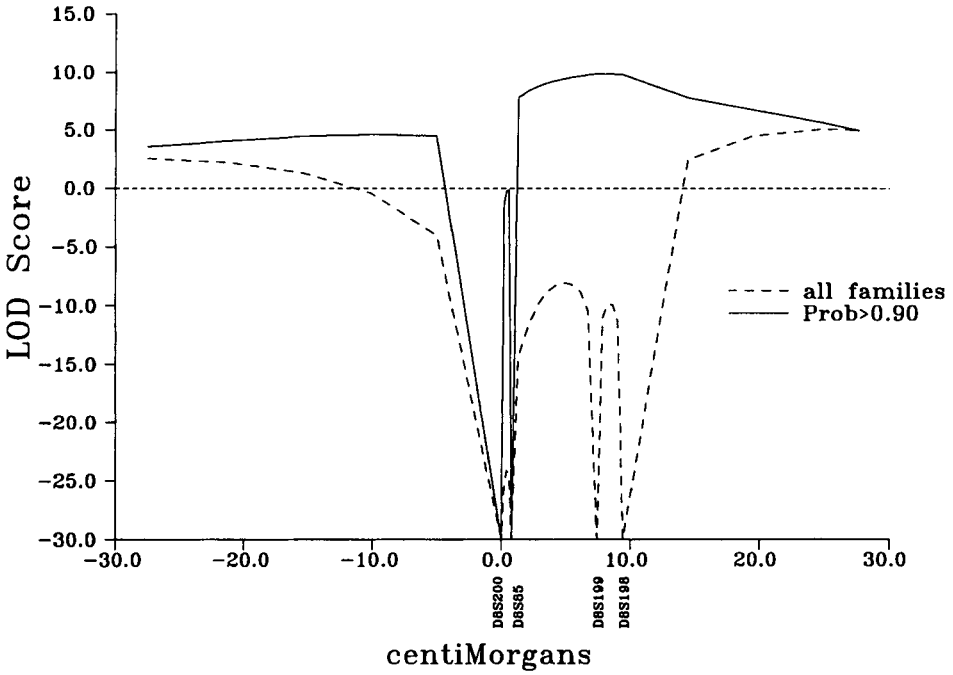

Fig. 3. Multipoint linkage map for chromosome 8 markers assuming 95% penetrance. The chromosome order is Cent-D8S200-D8S85-D8S199-D8S198-Telo.

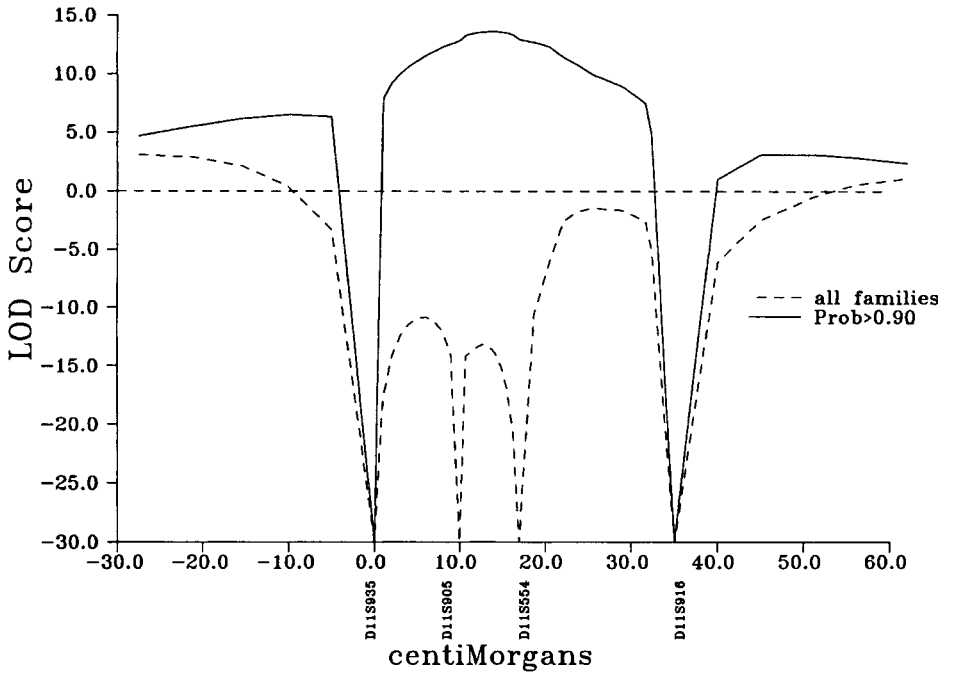

Fig. 4. Multipoint linkage map for chromosome 11 markers assuming 95% penetrance. The chromosome order is Telo-D11S935-D11S905-D11S554-D11S916-Cent.

TABLE V. Results of Homogeneity Testing of Multipoint Data With HOMOG3R

Hypothesis	Proportion of families linked to 8	11	Other	ln likelihood
Heterogeneity	0.50	0.50	0.00	45.96
	(0)[a]	0.60	0.40	25.84
	(0)	0.50	0.50	15.93
Homogeneity	(0)	(0)	0.0	
	(0)	(1)	(0)	0.0
	(0)	(0)	(1)	0.0

[a] Values in parentheses were held fixed.

TABLE VI. Conditional Probability of Linkage of Each Family to Chromosomes 8 and 11 as Calculated by HOMOG3R

Family	Chromosome 8	Chromosome 11
2	1.00	0.00
3	0.99	0.01
4	0.05	0.95
5	1.00	0.00
6	0.91	0.09
7	0.01	0.99
8	1.00	0.00
9	0.00	1.00
10	0.00	1.00
11	0.00	1.00
12	0.00	1.00
13	0.99	0.01

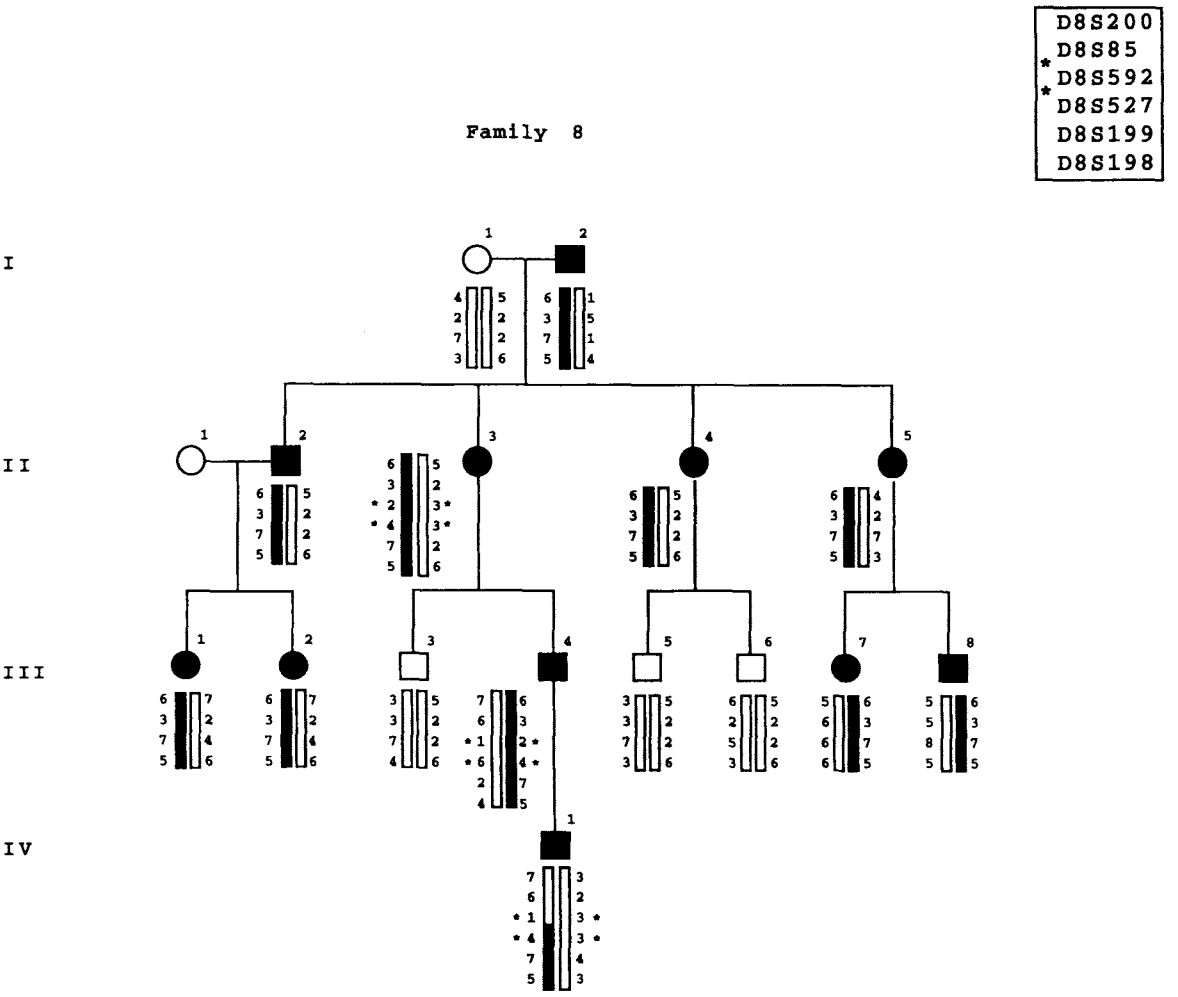

Fig. 5. Family 8 chromosome 8 haplotype. Haplotypes were reconstructed assuming the fewest number of recombinations. An * is used to indicate the markers which were typed in only a portion of the family to refine the location of the recombination.

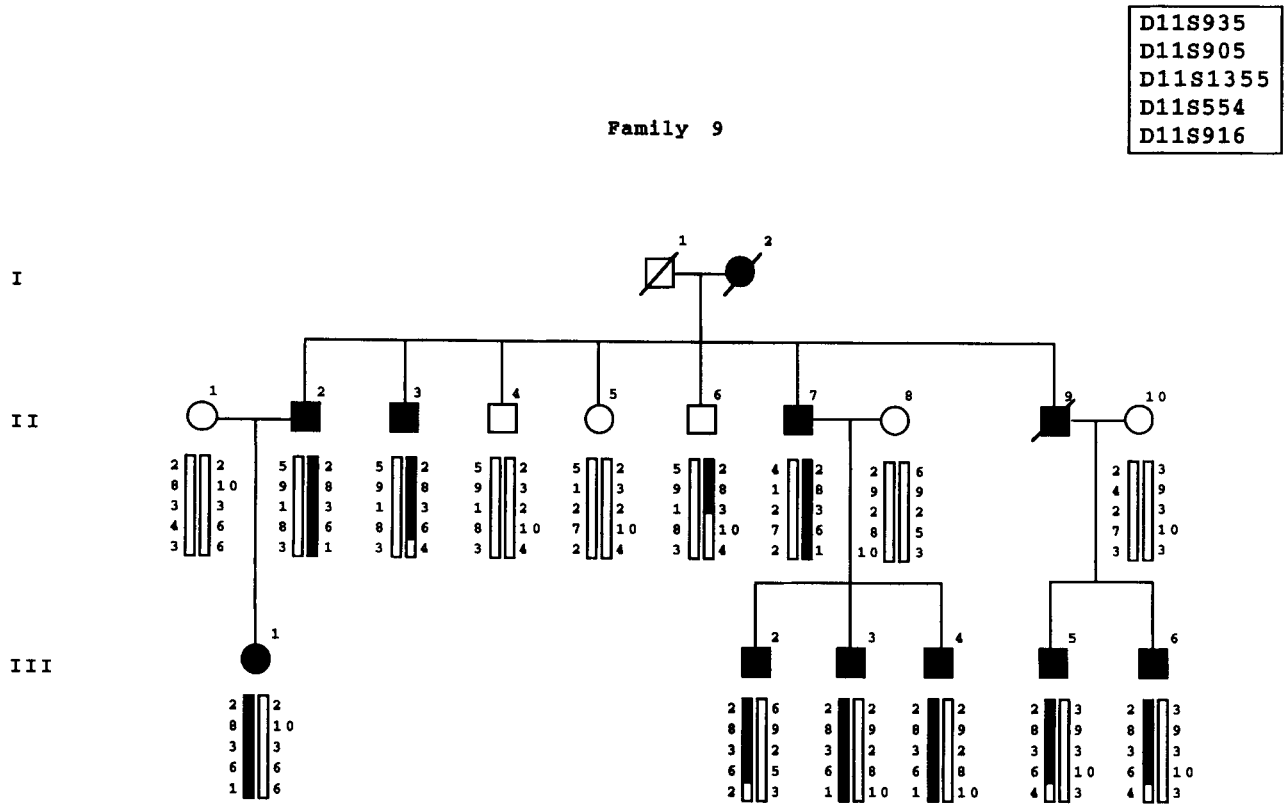

Fig. 6. Family 9 chromosome 11 haplotype. Haplotypes were reconstructed assuming the fewest number of recombinations.

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